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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
VANDERVEGT, FRANCOIS P	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/768,872	AHARONI ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- Th MAILING DATE of this communication app ars on th cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,18-20,32-39 and 157-165* is/are pending in the application.

4a) Of the above claim(s) *157-165* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,18-20 and 32-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10172003* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *12222003* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application is a continuation of PCT Application Serial Number PCT/US99/16747, which claims the benefit of the filing date of provisional application 60/093,859, and claims the benefit of the filing date of provisional application 60/101,825, and claims the benefit of the filing date of provisional application 60/102,960, claims the benefit of the filing date of provisional application 60/106,350, and claims the benefit of the filing date of provisional application 60/108,184.

Claims 1-15, 17, 21-31 and 40-156 have been canceled.

New claims 157-165 have been added.

Claims 16, 18-20, 32-39 and 157-165 are currently pending.

Claims 157-165 are withdrawn, as they are not drawn to the same invention as that of Group I, as elected by Applicant with traverse in the paper filed June 6, 2002.

Claims 16, 18-20 and 32-39 are the subject of examination in the present Office Action.

Response to Arguments

1. In view of Applicant's amendment filed October 17, 2003, all outstanding grounds of rejection are withdrawn. The following new grounds of rejection not necessitated by Applicant's amendment are being applied. Accordingly, the present Office Action is made NON-FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 16, 18-20 and 32-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Briefly, the claims are drawn to a "pharmaceutical composition" for the treatment of "an autoimmune disease." Claim 39 further provides an extensive list of autoimmune diseases characterized by different disease etiologies and reactivities to various autoantigens. The meaning of the term "pharmaceutical composition" is understood to imply a composition whose sole purpose is for

administration to a subject for the treatment of a condition. Accordingly, as a composition with a specified use, claims to a "pharmaceutical composition" must meet a level of enablement commensurate with that needed for a therapeutic method. The effectiveness of treating a response to an autoantigen is dependent on several factors, the most critical of which is whether the therapy can be used to treat an ongoing autoimmune response or whether it is only effective prophylactically (Tisch et al, Tisch, R et al. Proc. Nat. Acad. Sci. (USA). [1994] 91:437-438; U1 on form PTO-892, page 437, column 2, last paragraph in particular; newly cited). Typically, an autoimmune disease is diagnosed only after significant tissue damage has already occurred. Administration of antigen after pathogenic T cells have been activated may have an exacerbating effect on the disease, rather than a tolerogenic one. Another problem during the treatment of autoimmune diseases is determinant spreading during the course of the disease. The Tisch et al reference also teaches that "the high degree of specificity required for the process of clonal deletion/anergy may be limiting when dealing with diseases such as MS, IDDM, and RA, in which there are responses to several autoantigens [...] and the critical inciting autoantigen(s) is not known" (page 437, third full paragraph of column 3 in particular). The breadth of Applicant's claim is such that it recites a composition for the treatment of unrelated autoimmune diseases with a random-sequenced peptide terpolymer of a similar amino acid composition to myelin basic protein (MBP), an antigen related to the etiology of multiple sclerosis (MS) and the animal model experimental allergic encephalomyelitis (EAE). The specification demonstrates that prophylactic incubation of cells with the terpolymer inhibits T cell proliferation in response to MBP (Example 6) and inhibits a collagen-specific T cell response (Example 9). The specification does not, however, indicate that any of these diseases, including MS, could be successfully treated with the terpolymer of the invention, as in each case the examples show only prophylactic success in inhibiting a response of a previously characterized T cell line to a single well-defined antigen and does not address the effect of an ongoing autoimmune condition where reactivity is directed to multiple antigenic epitopes. For example, Example 10 of the instant specification shows that Copolymer 1 inhibits activation of T cells reactive with a single antigenic epitope of the acetylcholine receptor (AChR). However, myasthenia gravis is well known by practitioners to involve reactivity to a plurality of antigenic epitopes on the AChR, not a single epitope, and that the epitopes recognized can vary greatly between MG patients. Accordingly, based upon the lack of guidance in the instant specification, an artisan would not be able to predict any specific autoimmune diseases that would be treatable with a pharmaceutical composition of the present invention.

In view of the nature of the invention, the state of the art, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the

claims, it would take undue trials and errors to practice the claimed invention and this is not sanctioned by the statute.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially free" in claim 18 is a relative term that renders the claim indefinite. The term "substantially free" is not defined by the claim, the specification does not appear to provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, does the term refer to a function of the cited constituent or does it refer to the physical presence thereof? If referring to physical presence, what ratio or amount of the constituent constitutes an upper limit for "substantially free?"

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 16, 18-20 and 32-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Arnon, et al. (Israel J. Med. Sci. [1989] 25:686-689; cited by Applicant on form PTO-1449 filed July 5, 2002.

Arnon teaches COP 1, a synthetic basic random copolymer comprising A, E, K, and Y residues. Applicant is reminded that the term "comprising" in claim 16 is an open term that allows the inclusion of other elements that are not specifically recited in the claim, including glutamic acid residues. Additionally, the phrase "consisting essentially of" in claim 16 is being interpreted as being inclusive or open-ended, not excluding additional non-recited elements, i.e., "comprising," provided that the additional elements do not materially affect the basic and novel characteristic(s) of the claimed invention. Claim 18 is included because the term "substantially free" is a relative term that has not been adequately defined by the instant specification or claims as filed. Arnon teaches that alanine is present in the polymer at a molar ratio of 6.0, glutamic acid is present in the polymer at a molar ratio of 1.9, lysine is present in the polymer at a molar ratio of 4.7 and tyrosine is present in the polymer at a molar ratio of 1.0

(Abstract in particular). Given that the sum of the molar ratios is 13.6, alanine is present as a molar fraction of 0.441, lysine is present as a molar fraction of 0.346 and tyrosine is present as a molar fraction of 0.140 [claim 19]. Claim 20 is included because the term "about" is a relative term and the metes and bounds of the term have not been established by the specification. Accordingly, 0.441 satisfies the recitation of "about 0.54," 0.346 satisfies the recitation of "about 0.35" and 0.140 satisfies the recitation of "about 0.10." Arnon teaches that COP 1 was effective in exerting a suppressive effect on EAE when injected into guinea pigs when administered in an aqueous saline solution, a pahramaceutically acceptable carrier (page 686, second column in particular). Arnon further states that COP 1 is effective in suppressing EAE in rabbits, mice, rhesus monkeys and baboons (page 686, second column in particular). The prior art teaching anticipates the claimed invention.

Claims 32 and 33 are included because, while Arnon does not specifically teach the size of COP 1, it is noted that it is a randomly arranged synthetic polypeptide product and the final size of the product will be determined by the amounts of the individual constituent amino acid residues added to the reaction mixture and the time the reaction is allowed to run. Further, in order to exert its effect on T cells, the peptide must be processed into small 8-20 amino acid residue long epitope peptide, irrespective of the stating size of the polypeptide. Accordingly, provided that the ratio of the elements is maintained in the synthesis of the polypeptide, the beginning size of the polymer is not seen as being patentably distinct.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 16, 18-20, and 32-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Teitelbaum et al (Proc. Nat. Acad. Sci. [1988] 85(24):9724-9728; cited by Applicant on form PTO-1449

filed July 5, 2002) in view of Arnon, et al. (Israel J. Med. Sci. [1989] 25:686-689; cited by Applicant on form PTO-1449 filed July 5, 2002).

Teitelbaum teaches Cop 1, a 21,000 dalton [claim 32] synthetic basic random copolymer comprising A, E, K, and Y residues. Applicant is reminded that the term "comprising" in claim 16 is an open term that allows the inclusion of other elements that are not specifically recited in the claim, including glutamic acid residues. Additionally, the phrase "consisting essentially of" in claim 16 is being interpreted as being inclusive or open-ended, not excluding additional non-recited elements, i.e., "comprising," provided that the additional elements do not materially affect the basic and novel characteristic(s) of the claimed invention. Claim 18 is included because the term "substantially free" is a relative term that has not been adequately defined by the instant specification or claims as filed. Teitelbaum teaches that alanine is present in the polymer at a molar ratio of 6.0, glutamic acid is present in the polymer at a molar ratio of 1.9, lysine is present in the polymer at a molar ratio of 4.7 and tyrosine is present in the polymer at a molar ratio of 1.0 (Abstract in particular). Given that the sum of the molar ratios is 13.6, alanine is present as a molar fraction of 0.441, lysine is present as a molar fraction of 0.346 and tyrosine is present as a molar fraction of 0.140 [claim 19]. Claim 20 is included because the term "about" is a relative term and the metes and bounds of the term have not been established by the specification. Accordingly, 0.441 qualifies as "about 0.54," 0.346 qualifies as "about 0.35" and 0.140 qualifies as "about 0.10." Teitelbaum teaches that Cop 1 was effective in specifically inhibiting T cell responses to myelin basic protein, which is a target autoantigen in the inflammatory autoimmune disease multiple sclerosis and in the experimental allergic encephalomyelitis (EAE) model (see entire publication).

Teitelbaum teaches that Cop 1 may be effective for the *in vivo* treatment of multiple sclerosis, but does not teach an "effective amount" in a pharmaceutically acceptable carrier.

Arnon et al teaches that the administration of Cop 1 to rhesus monkeys and baboons even after the onset of clinical symptoms of EAE demonstrated reversal of disease symptoms and full recovery (paragraph bridging pages 686-687 in particular). Arnon further teaches that the use of Cop 1 in human subjects improved the disability status of the subjects and reduced exacerbation versus placebo-treated controls (paragraph bridging pages 688-689 in particular). Accordingly, Arnon teaches the use of an effective amount of Cop 1.

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to formulate an effective amount of the Cop 1 copolymer of Teitelbaum in a pharmaceutically acceptable carrier with a reasonable expectation of success because Arnon teaches that

it improves the clinical status of non-human EAE subjects and human multiple sclerosis patients. One would have been motivated to use this compound in a pharmaceutical preparation by the teaching of Arnon that Cop 1 is related to the encephalogenic myelin basic protein but is not itself encephalogenic.

Claim 33 is included because, while Teitelbaum teaches that Cop 1 is 21Kd in size, it is noted that it is a randomly arranged synthetic polypeptide product. Further, in order to exert its effect on T cells, the peptide must be processed into small 8-20 amino acid residue long epitope peptide, irrespective of the stating size of the polypeptide. Accordingly, provided that the ratio of the elements is maintained in the synthesis of the polypeptide, the beginning size of the polymer is not seen as being patentably distinct.

Conclusion

4. The reference cited on form PTO-1449 filed on October 17, 2003 has been noted as considered but has been lined through because it would not be proper to list an unrelated provisional application on the front page of any patent that may issue from the instant application.

5. Claim 20 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571)272-0852. The examiner can normally be reached on M-Th 6:30-4:00; Alternate Fridays 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (571) 272-0841.Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
January 14, 2004

PATRICK J. NOLAN, PH.D.
PRIMARY EXAMINER
1/25/04